Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing COPD Treatment

April to June 2022

Background

- Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease characterized by persistent bronchial obstruction and respiratory symptoms such as dyspnea, chronic cough, and sputum production. Chronic airway inflammation plays a key role in the pathogenesis of COPD, causing narrowing of the small airways, mucus hypersecretion, and destruction of the lung parenchyma. Damage to the walls of the lungs leads to reduced elasticity, and reduces the ability to exhale.
- Pharmacological therapy for COPD is used to reduce symptoms (e.g. dyspnea, cough, sputum), improve exercise tolerance and quality of life, and prevent the occurrence/reduce the severity of acute exacerbations (AECOPD).
  - ◊ Reducing AECOPD may reduce ER visits/hospital admissions and mortality.
- Long-acting bronchodilators are the cornerstone of treatment for COPD and generally should be optimized before starting therapy with inhaled corticosteroids (ICS) therapy.
- Each pharmacological treatment regimen should be individualized and guided by the severity of the symptoms, risk of exacerbations, response to therapy, side effects, and comorbidities.

For quarterly medication reviews from **April to June 2022,** identify residents currently receiving treatment for COPD.

- Review their symptoms, the occurrence of AECOPD in the past 12 month, and their use of short-acting bronchodilators (e.g. salbutamol) in the past 3 months to estimate the effectiveness of their current COPD management.
- If the resident's respiratory diagnosis isn't clear, consider consulting respirology or respiratory therapist (RT), as available
- Assess the effectiveness of their current COPD management
  - ◊ Has therapy with bronchodilators been optimized?
  - ◊ If currently on a ICS containing regimen, assess if treatment with an ICS is warranted or if a stepwise withdrawal of the ICS can be attempted.
  - ◊ Is the resident able to effectively use the current inhaler device? If not, consider switching to an alternate device/ medication in the same class or consult RT, if available, to assess and make device recommendations. Refer to the attached COPD treatment resources.
  - ◊ Reassess any therapy changes made in the past 6 months for bronchodilators and 12 months for ICS combinations.[1]
  - ◊ Dependent on the resident's symptoms, lung function, and risk of exacerbations, consider if a treatment step up or step down is warranted. Refer to Figure 1 on page 2 for guidance.
- Assess the resident's future risk of AECOPD
- Assess if the resident is experiencing any side effects (e.g. thrush, pneumonia in the past year, throat irritation, dry mouth).
- Identify residents who smoke tobacco or medical cannabis
  - ◊ Smoking cessation can help slow lung function decline, decrease symptoms, reduce the risk of pneumonia, reduce the frequency/severity of AECOPD and hospitalizations, and prolong survival time of patients. Refer to regional smoking cessation or tobacco use resources.

COPD Treatment: GOLD 2021 Guidelines[2]

- **Bronchodilators**: Patients with COPD who experience more than occasional dyspnea should be prescribed long acting bronchodilator therapy. Long-acting beta agonists (LABAs) and long acting muscarinic antagonists (LAMAs) significantly improve lung function, dyspnea, health status, and reduce exacerbation rates. However LAMAs have been shown to have a greater effect on exacerbation reduction compared with LABAs. (Evidence A)
  - ◊ For those with persistent COPD symptoms while taking one long-acting bronchodilator, treatment should be escalated to two bronchodilators (e.g. LAMA + LABA)
- **Inhaled corticosteroids** are not recommended as monotherapy in COPD. Combination agents containing inhaled corticosteroids (ICS) along with long-acting beta agonists (e.g. ICS/LABA) or triple inhaled therapy (LAMA/LABA/ICS) are considered appropriate step-up therapy for patients experiencing continual or worsening COPD symptoms and exacerbations despite appropriate therapy with long-acting bronchodilators.

For the full GOLD 2021 Guidelines, see GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf (goldcopd.org)

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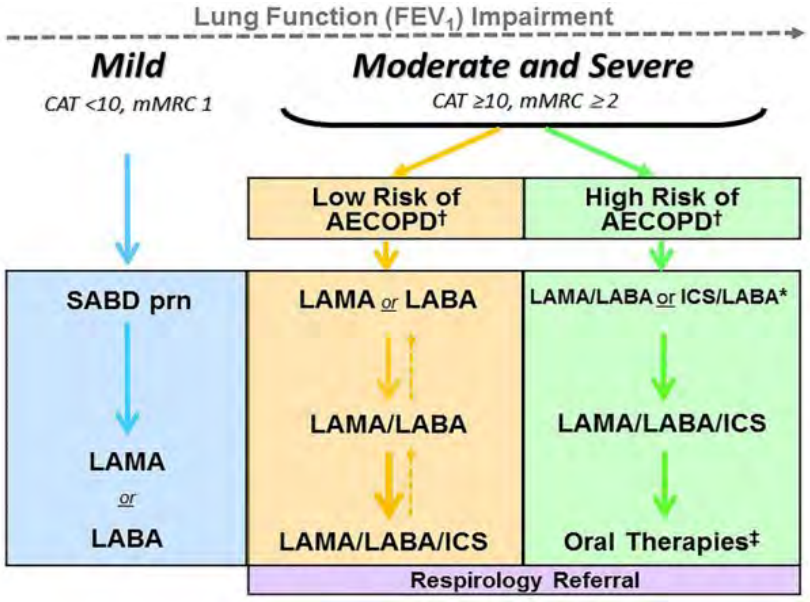
Canadian Thoracic Society (CTS) Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019[1]

- A significant update from the 2017 guidelines is the recommendation of ***dual inhaled therapy (LAMA/LABA or ICS/LABA) as first line treatment*** in patients with moderate to severe COPD with a high risk of AECOPD.
  - ◊ LAMA/LABA is the preferred choice except in patients with previous exacerbations who have higher peripheral eosinophilia (300 cells/µL or higher).
- There was no change from the 2017 guidelines for patients with COPD and concomitant asthma. Initial therapy with low-moderate dose ICS/LABA is recommended. If needed for symptom control or increased exacerbations, the dose of ICS/LABA can be increased and/or a LAMA added. Step down should be considered if there is no improvement.
- Included in the guidelines is an updated COPD pharmacologic algorithm. (See Figure 1 below)
- Treatment escalation is supported by evidence that inhaled combined therapy is superior to monotherapy, and triple therapy to dual therapy for managing symptoms and preventing AECOPD in certain patient populations.
- *The risk/benefit of adding ICS must be assessed for each patient prior to stepping up treatment.*
- As the superiority of combination inhaler therapy may not be achieved in every patient, step down (deprescribing) may need to be considered. Step down treatment necessitates close monitoring of symptoms, exacerbations, and lung function. Withdrawing ICS may lower health status and lung function in some patients.
  - ◊ Example: Step down may be cautiously considered in stable COPD patients with no improvement in dyspnea or health status despite a step up to dual or triple combination therapy.
- Although there is no absolute time interval at which the evaluation should be performed following a change in therapy, 6 months after initiating a long acting bronchodilator and 12 months after initiating a combination regimen with an ICS are suggested timeframes.

For the full Clinical Practice Guideline[1], go to https://cts-sct.ca/wp-content/uploads/2019/10/CTS-COPD-Rx-2019-Guideline_Final.pdf



†Patients are considered at **low risk of AECOPD** with 1 or less moderate AECOPD in the last year (moderate AECOPD is an event with prescribed antibiotic and/or oral corticosteroids), and did not require hospital admission/ED visit.

High Risk of AECOPD with 2 or more moderate AECOPD or 1 or more severe exacerbation in the last year (severe AECOPD is an event requiring hospitalization or ED visit)

*Blood eosinophil 300/µL in patients with previous AECOPD may be useful to predict a favorable response to ICS combination inhaler.

Figure 1. COPD pharmacotherapy promoting an approach that aligns treatment decisions with symptom burden and risk of future exacerbations[1]

Abbreviations: CAT: COPD assessment test; **mMRC**: Modified Medical Research Council; **SABD** prn: short-acting bronchodilator as needed; **AECOPD**: Acute Exacerbation of COPD; **LAMA**: Long-acting muscarinic antagonist; **LABA**: Long-acting ß2-agonist; ICS: Inhaled corticosteroid. mMRC is a modified (0-4 scale) version of the MRC breathlessness scale which was used in previous CTS guidelines. The mMRC aligns with the Global Initiative for Chronic Obstructive Airways Disease (GOLD) report[2].

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ICS Treatment for COPD

- COPD guidelines only recommend ICS as an add-on therapy to long-acting bronchodilator therapy– not as monotherapy.[1,2]
  - ◊ ICS monotherapy in patients with COPD increases mortality (NNH=87 per year) compared to ICS/LABA (TORCH trial).[9]
- While only a select number of patients with COPD will benefit from ICS, up to 70% of COPD patients in current practice receive ICS therapy[4] (usually as a fixed combination with a LABA).
- ICS-containing regimens are not recommended in patients at low risk of AECOPD. Patients with mild-to-moderate airflow obstruction on spirometry and infrequent exacerbations may experience greater risks than benefits.[5]
- High-dose ICS proved to be no better than low-dose for reducing exacerbations (ETHOS trial). [9]

What is the evidence for using ICS for COPD?

- Evidence is conflicting for ICS efficacy in COPD: results of the WISDOM trial suggested ICS had little benefit whereas other trials have showed that ICS decreased exacerbations. [9]
  - ◊ TORCH trial, ***NNT = 44 patients needed to be treated for 3 years to prevent 1 exacerbation***
  - ◊ INSPIRE trial, ***NNT= 83 patients needed to be treated for 2 years to prevent 1 exacerbation***
- Studies have compared ICS containing therapy to LAMA and/or LAMA/LABA therapy to compare efficacy at preventing AECOPD.[4,5,6]
  - ◊ There is evidence that the LABA/LAMA combination further reduces severe exacerbations compared to LABA/ICS combination in the high-risk population[3] (network HR 0.78 (95% CI 0.64 to 0.93).
  - ◊ INSPIRE showed that ICS/LABA was no more effective than a LAMA at preventing exacerbations in patients with severe COPD.
  - ◊ The FLAME trial, which was conducted in higher exacerbation risk patients, showed superiority for LAMA/LABA over ICS/LABA for exacerbation prevention over 1 year (note: in the FLAME trial, patients with past diagnosis of asthma were excluded).[10]
  - ◊ While TORCH was a landmark trial showing significantly fewer exacerbations, slower rate of decline in lung function, and improved health status with ICS/LABA combination, post hoc analysis showed that the benefits were mainly due to the LABA.
  - ◊ A meta-analysis showed that ***38 patients had to be treated for 1 year with a LAMA/LABA/ICS to prevent one exacerbation when compared to LABA/LAMA combination therapy***. [11]
- In the CORTICO-COP trial, there is suggestion that patients with blood eosinophils 300 or higher may receive greatest benefit from ICS, but evidence is limited to subgroup analyses and limited testing in random controlled trials.[9]
  - ◊ The person-based NNT per year of LAMA/LABA/ICS combination therapy *versus* LABA/LAMA combination therapy was significantly ($p<0.05$) lower in patients with eosinophil counts 300 cells/µL or higher (NNT = 8.58) than in those with counts less than 300 cells/µL (NNT = 46.28). [11]

What are the side effects of ICS therapy?

- There is evidence that the LABA/ICS combinations increase the odds of pneumonia compared to LAMA/LABA combinations, LAMA, and LABA treatments in the low-risk and high-risk population[3].
  - ◊ TORCH ***NNH = 16 patients for 3 years to cause 1 pneumonia (remember NNT = 44 to prevent 1 exacerbation)***
  - ◊ INSPIRE ***NNH = 22 patients for 2 years to cause 1 pneumonia (remember NNT = 83 to prevent 1 exacerbation)***
  - ◊ The impact of ICS on pneumonia risk is apparent within the first year of use and remains elevated over periods of continued use.
  - ◊ A cohort study of patients with COPD showed that ICS discontinuation was associated with a 37% reduction in the risk of serious pneumonia[4].
- Other adverse effects of ICS therapy include dysphonia, skin bruising, and oral candidiasis.
- ICS therapy may also increase the incidence of cataracts, and diminish bone density[5]. These adverse effects appear to be more common at higher doses.

Which residents with COPD should be treated with ICS?

- As treatment with ICS has not shown to be superior to long acting bronchodilators in all studies, and given that long term ICS use is associated with potentially severe adverse effects, identifying residents who will benefit from ICS treatment is warranted to avoid unnecessary exposure.

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What about triple therapy (LAMA/LABA/ICS) inhalers?

- The IMPACT trial is a randomized controlled trial that provided evidence that COPD exacerbation risk was decreased in patients using LAMA/LABA/ICS compared with an ICS/LABA or LAMA/LABA.
- The design of the IMPACT trial has raised some methodological issues that may limit the interpretation of its findings.
  - ◊ More than 70% of the participants were receiving an ICS prior to the trial, and patients with a history of asthma were included in the trial.
  - ◊ Many of the patients who were assigned to the LAMA/LABA group were actually stepping down in their treatment when they had their pre-study inhaled glucocorticoid abruptly withdrawn at the start of the trial.
  - ◊ The inclusion of patients with past asthma and the withdrawal of ICS in patients for whom ICS was indicated could potentially explain the rapid surge in exacerbations observed in the first month after randomization in the LAMA/LABA group
  - ◊ During the subsequent 11 months of follow-up, the incidence of exacerbation with LAMA/LABA was practically identical to that with LAMA/LABA/ICS group. [10]
- This suggests that there is a subset of patients who could benefit from triple therapy, while the others would benefit at least equally from LAMA/LABA.
- Triple therapy should be limited to patients with more severe COPD symptoms that cannot be adequately managed by dual therapy.
- The only triple therapy inhaler currently marketed, Trelegy Ellipta (fluticasone furoate/ umeclidinium/vilantero), requires part 3 EDS application for patients who are not controlled on optimal dual inhaled therapy for COPD

Factors to consider when initiating ICS treatment in combination with one or two long acting bronchodilators (note the scenario is different when considering ICS withdrawal)

Strong Support	Consider Use	Against Use
• History of hospitalization(s) for exacerbations of COPD[#2] • 2 or more exacerbations of COPD per year[# 2] • Residents at high risk of AECOPD who remain symptomatic[#1,2,3] • Blood eosinophils* of 300 or more cells/µL [2] • History of or concomitant asthma [1,2]	• 1 moderate exacerbation of COPD per year[#2] • Blood eosinophils* 100-300 cells/µL in patients • 2 or more moderate exacerbations/year OR 1 more severe exacerbations [2]	• Repeated pneumonia events [2] • Blood eosinophils* less than 100 cells/µL • History of mycobacterial infection [2]

#despite appropriate long-acting bronchodilator maintenance therapy

**Blood eosinophils should be seen as a continuum and counts are likely to fluctuate. Airway eosinophilia is a hallmark inflammatory response in asthma and is involved in the airway inflammatory process in COPD. Blood eosinophil counts might reflect degree of sputum eosinophilia which is increased in some patients with AECOPD*

Is it safe to deprescribe ICS[4,5,6]?

- Studies and recommendations support the withdrawal of ICS therapy in a large group of patients with COPD.
- The INSTEAD trial illustrated that even mono-bronchodilation may be sufficient to allow for ICS withdrawal in a low risk group.
- The WISDOM, OPTIMO and DACCORD trials confirmed that ICS can be withdrawn, even for those with severe to very severe COPD, without increased risk of exacerbations provided appropriate bronchodilator treatment is initiated.
- The WISDOM study provides a clear de-escalation schedule that isolates the ICS component from the triple treatment and then gradually reduces the ICS dose. Their findings suggest that even patients with severe COPD and a high-risk of exacerbations can be safely withdrawn from ICS therapy as long as they are clinically stable and maintained on background long-acting bronchodilators.
- Careful monitoring is essential since withdrawal of ICS can decrease lung function or increase exacerbation risk in some patients. WISDOM and SUNSET subgroup analysis showed that individuals with an blood eosinophilia count of 300 cells/µL or higher may be more susceptible to exacerbations after ICS withdrawal.
- Monitoring should include self-report or nurse observation of breathlessness, number of puffs of salbutamol, or other interventions required. See *Sample Dyspnea Monitoring Tool* attached.

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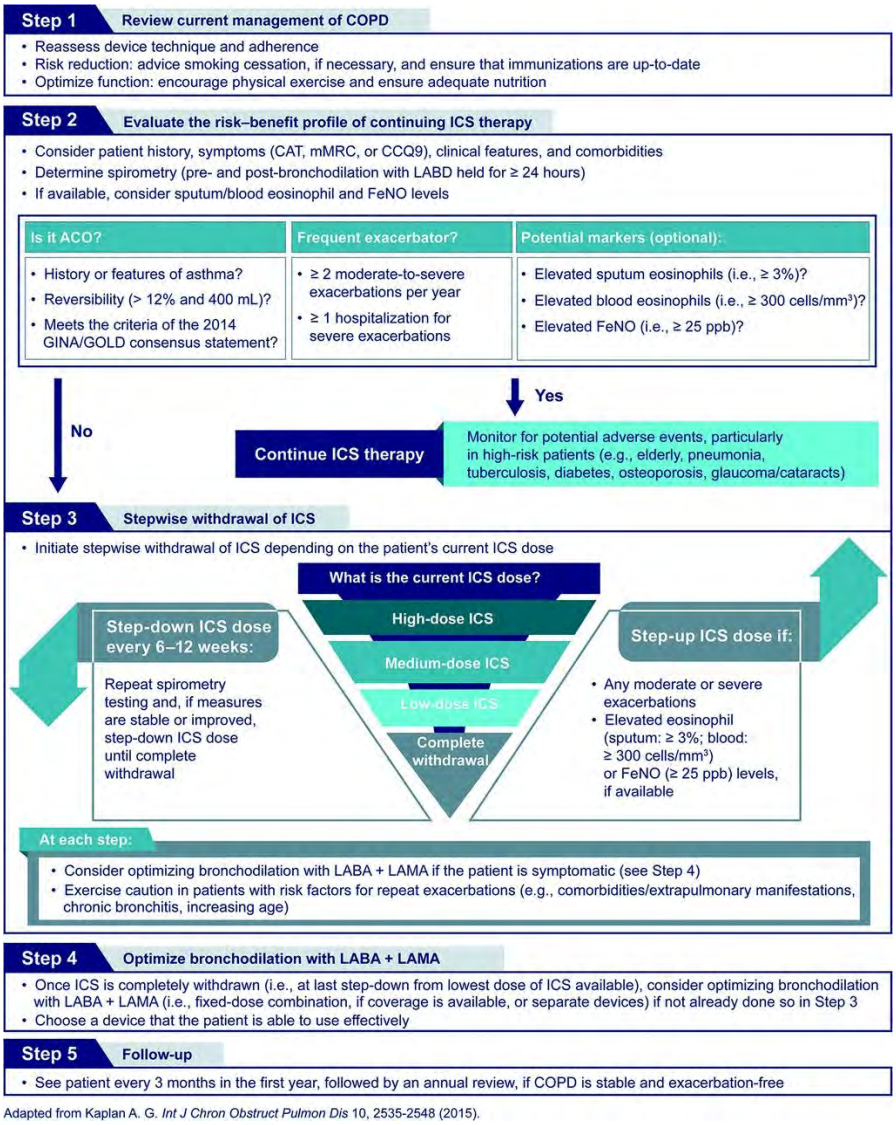
- Deprescribing of inhaled ICS should be considered if [1,2,5]:
  - ◊ ICS therapy was started without a clear indication (e.g. no history of exacerbations)
  - ◊ There is no history of asthma
  - ◊ There is a lack of clinical benefit after 1 year (e.g. no improvement in the frequency of exacerbations, no improvement in symptoms such as dyspnea)
  - ◊ Side effects are occurring (e.g. recurrent episodes of pneumonia)
- Deprescribing inhaled ICS could be considered if:
  - ◊ If there has been no exacerbations in the past year[5]
  - ◊ No decline after switching from high to low ICS dose[4]

Applying the wisdom of stepping down inhaled corticosteroids in patients with COPD: a proposed algorithm for clinical practice[7]

- Abrupt cessation of chronic corticosteroid therapy can precipitate rebound systemic effects, therefore a stepwise withdrawal is recommended to reduce the potential risk of steroid effects.
- A step-by-step algorithm is proposed for real-life clinical practice to answer the following questions (see Figure 2 below):
  1) In which patients is ICS withdrawal safe?
  2) How to withdraw ICS in appropriate patients?
  3) How to follow up?

Figure 2 : A proposed step-by-step algorithm for safely withdrawing ICs from patients with COPD in real-life clinical practice.[7]

Abbreviations: ACOs, *asthma–COPD overlap syndrome;* ***CAT,*** *COPD Assessment test;* ***CCQ9,*** *Chronic COPD Questionnaire;* ***COPD,*** *chronic obstructive pulmonary disease;* ***FeNO****, fractional exhaled nitric oxide;* ***GINA****, Global Initiative for Asthma;* ***GOLD,*** *Global Initiative for Chronic Obstructive Lung Disease;* ***ICs****, inhaled corticosteroids;* ***LABA****, long-acting β2-agonist;* ***LABD,*** *long-acting bronchodilator;* ***LAMA****, long-acting muscarinic antagonist;* ***mMRC****, modified Medical Research Council Dyspnea Scale;* ***ppb****, parts per billion.*



Adapted from Kaplan A. G. *Int J Chron Obstruct Pulmon Dis* 10, 2535-2548 (2015).

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Generic Fluticasone-Salmeterol Inhalers

- For the 2020-2021 fiscal year, there were 1,305 prescriptions for fluticasone-salmeterol inhalers filled for Manitoba PCH residents, resulting in a cost of $164,385.
- Two generic fluticasone-salmeterol Diskus Dry Powder Inhalers (DPIs) are now available.
  - ◊ pms-Fluticasone Propionate/Salmeterol DPI (which has a similar diskus design to Advair)
  - ◊ Wixela Inhub: nurses can familiarize themselves with the use of this device at https://www.wixela.com/en/how-to-use
  - ◊ Similar to Advair, these inhalers are in a foil package. The foil package should not be opened until the inhaler is required for use. To ensure the inhaler is labeled for each specific resident, pharmacy will include a truncated label that is to be applied to the inhaler when the foil is opened. A **beyond-use date of 30 days** needs to be added after the foil package is opened. The inhaler can be used until the dose counter reads "0" or 30 days after it was removed from the foil, whichever comes first.
- Spacer devices (e.g. Aerochambers) are not to be used with dry powder inhalers.
- These generic versions of Advair Diskus are covered by Pharmacare at a significant cost savings, at approximately 50% the cost of Advair.

Recommendation: For PCHs serviced by community pharmacies, consider switching residents on fluticasone-salmeterol MDI plus spacer to the generic fluticasone-salmeterol inhalation powder.

What is the impact of the COVID-19 pandemic on patients with COPD?

Addressing Therapeutic Questions to Help Canadian Health Care Professionals Optimize COPD Management for Their Patients During the COVID-19 Pandemic[8]

- The Position Statement was put forth by the Canadian Thoracic Society (CTS) COPD Assembly Steering Committee.
  - ◊ Based on what is known about viral respiratory infections in patients with COPD, optimal pharmacological treatment is the best way to prevent exacerbations and/or reduce the severity of exacerbations secondary to COVID-19.
- It is recommended that MDIs with spacing devices, soft mist inhalers, or dry powder inhalers be used to administer all COPD medication in all clinical circumstances.

For the full position statement, please go to https://cts-sct.ca/wp-content/uploads/2020/05/CJRCCSM_Addressing-therapeutic-questions-to-optimize-COPD-management-during-the-COVID-19-pandemic.pdf

Nebulization of medication is considered an aerosol generating medical procedure (AGMP), strategies to reduce the risk from AGMPs have been outlined including:

- Carefully analyze risks and benefits to AGMPs; avoid performing unnecessary AGMPs
- Consider alternative to AGMPs

LTC residents receiving bronchodilators and steroids via nebulization will continue to be converted to MDIs administered via a spacer device with mask unless "no substitution" is indicated by the prescriber as part of the order and the reason for not substituting. For more information, refer to the COVID-19 Provincial Guidance for Aerosol Generating Medical Procedures (AGMPs)

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